BLA Supplement 103964-0
CLINICAL REVIEW

1.0 GENERAL INFORMATION

Applicant: Hoffman LaRoche

Product: Generic: Pegylated Interferon
Trade: Pegasys™

Route: Subcutaneous

Indication: Treatment of Hepatitis C Infection

Related BLAs: BLA 99-2672

Milestone Dates:

Date of Original BLA filing: May 19, 2000
Date Complete Response Letter issued: April 10, 2001
Date Response to Complete Response received: April 15, 2002

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2.0 CLINICAL REVIEW OF SPONSOR SUBMISSION (RESPONSE TO FDA COMPLETE RESPONSE)

History

Following initial submission of their Biologics License Application for their pegylated interferon product (Pegasys), the initial Agency review culminated in a Complete Response (CR) letter. The CR letter outlined several deficiencies, issues and questions that required a response from the sponsor before review of the BLA would continue. The sponsor has submitted this package of information in an effort to comply with this request.

This review will address the clinical issues raised in the CR letter. These issues began with item 50 in the CR letter. The sponsor has chosen to respond item by item and has used the same numbering in their responses as used in the CR letter.

Review of Responses to Items in Complete Response Letter

The numbering in the review will also use the same numbering as in the original CR letter. First, the original question from the CR letter will be quoted, followed by a summary of the response by the sponsor. Finally, where applicable, reviewer comments will be added:

50. Your submission includes results following response determinations made by a review board. We note that the review board's response rates for patients receiving peginterferon alfa-2a were higher than when protocol defined response criteria were used. Please be aware that we consider the protocol defined response criteria as the more valid and appropriate set of criteria for this application and will cite the protocol-defined response rates in product labeling.

The sponsor responded to this item by proposing an entirely new endpoint with which to assess the data from the Pegasys clinical development program. This endpoint would be modeled on specific and detailed case definitions for sustained viral response that have subsequently been used in the sponsor's separate Pegasys + Ribavirin program. The case definitions differ between the two programs with regards to the timing of sampling for the presence of virus. The sponsor argues that re-defining the endpoint of the Pegasys trials to match the Pegasys+ Ribavirin trials would allow for a more consistent presentation in the label of the results of the Pegasys versus Pegasys + Ribavirin studies. By chance, re-defining the endpoints also results in an improvement in the efficacy results for Pegasys by increasing the rate of sustained viral response.

<u>Reviewer Comment</u>: For nearly 3 years, this sponsor has advocated proposal after proposal to alter the fundamental response rates induced by the Pegasys product. In every post-hoc attempt to re-define the response rate, the end result has been to indicate a response rate of the product beyond the rates shown in the protocol-defined outcome measures. Each time the sponsor has argued that these post-hoc efforts somehow better represent what the product "really" does for patients with hepatitis C. The latest proposal is consistent with this continuous lobbying effort. ----------

While it is a noteworthy goal to have the product label be easy to follow, the fact is that these two clinical trials and clinical programs were performed at different times and were never intended a priori to be merged as the sponsor proposes.

The fact that the sustained viral response rates for Pegasys in both programs fall within each other's confidence intervals represents another reason to not deviate from current plans to use the protocol-defined outcomes in the product label. The most unbiased representation of the data from the Pegasys clinical trials program remains the use of the original protocol-defined outcome measure for sustained viral response.

51. Although pegylated interferons are associated with a remarkably high number and frequency of certain adverse events including flu-like symptoms, depression and other CNS related adverse events, you state that treatment with the product was associated with better quality of life and less fatigue than that observed in the control groups. Please elaborate on your statement and the apparent inconsistencies between the adverse event profile and your conclusions about improved quality of life with your product.

The sponsor responded by acknowledging that treatment with Pegasys causes a decrease in the Health Related Quality of Life score compared to pre-treatment scores. They argue that the decrease was not as much as that caused by the standard interferon treatment arm of the trials.

<u>Reviewer Comment</u>: Because of the inherent bias that could exist with any quality of life score, it is critical that the patient be blinded to treatment regimen. In this setting the use of a placebo control for Pegasys recipients on days when control patients were receiving standard interferon would have been an example of an acceptable option to possibly ascertain any difference in the use of Pegasys on this endpoint. Because of the lack of such safeguards to remove bias, the quality of life findings from these studies are too suspect to be included as valid findings from these studies.

52. Please provide additional relevant data regarding deaths on or proximal to the study due to or involving opiate overdose in peginterferon alfa-2a treated patients. These data
should include physician hospital summaries, autopsy findings, other physician generated summary documents characterizing the clinical findings and the clinical course and management of the following patients:

    a. NV15489, #18265/0106

    b. NV15496, #20881/1361

    c. NV15495, #20561/0369

    d. NV15497, #20983/2689

    e. NV15942, #2335 (site number not provided in SAE report)

    In addition, please provide copies of source data from toxicology testing for all of the listed patients.

The sponsor provided extensive details surrounding the overdose deaths in the Pegasys clinical trials. Information included autopsy reports, psychiatric and other medical reports and a narrative summary on each patient.

<u>Reviewer Comment</u>: The data on each of the events confirm that each of the deaths were due to drug overdose. Other than the temporal relationship between receipt of Pegasys and the overdose event, in 4 of the 5 deaths there does not appear to be any contribution of the product to the events leading up to each overdose event. In each of these four cases (# 0106, 1361, 0369 and 2689), the sponsor presented evidence of other contributing factors (mostly severe personal emotional problems) that likely had a significant impact on the patient and resulted in the use of resumption of prior use of narcotic substances. In only one of the cases (2335), the sponsor was unable to convincingly discount the possible influence of pegylated interferon at least indirectly, possibly through initiation of the known induction of depression, on the patient's return to IVDU. On the other hand, there was no depression or any other source of change in patient 2335 that could be uncovered to adequately gauge whether Pegasys was or was not involved with the resumption of this patient's use of narcotics.

Please see question 53 discussion regarding the new, relevant information concerning the expected background event rates of overdose deaths in the HCV IVDU population. Given the new information provided by the sponsor in question 53 and the lack of any firm relationship (other than temporal) between receipt of Pegasys and onset of events leading to overdose, the overdose deaths cannot be generically attributed to receipt of Pegasys.

53. Some former opiate addicts who had been in recovery for several years appeared to quickly resume their addictive behavior after receiving peginterferon alfa-2a. Specifically patient #18265/0106 had been without opiates for 8 years and died of an opiate overdose within 138 days of starting peginterferon alfa-2a. Also, patient #2335 had been without opiates for 10 years and died of an opiate overdose within 31 days of starting peginterferon alfa-2a. Please comment on the possible association between use of peginterferon alfa-2a and relapse of drug addiction. Please discuss the types of additional data, including drug interaction studies, that may help address this possible association (see comment 56, below).

The sponsor responded to this issue by performing a literature review of studies performed that investigated the natural history of patients with hepatitis C. These studies were very informative in providing information about the possible "background" incidence of deaths due to overdose in the hepatitis C population. The most valuable of the references was Thomas DL, JAMA. 2000; 284:450-456). In this study, over 1600 patients with hepatitis C and who also were intravenous drug users (IVDU) were followed for a median of 9 years. It was determined that there was an incidence of 78 deaths due to overdose in this patient population (1667 patients followed for 9 years), for an event rate of 5 per 1000 patient-years. The other studies cited had a mix of HCV patients with varying percentages who were also IVDU. In these studies the background rate of deaths due to overdose ranged from 0.6 – 1.3 deaths per 1000 patient years.

Re-examination of the data from the Pegasys BLA revealed the following rate of deaths due to overdose:

5 deaths in 2215 patients (from both the sponsor's PEG-IFN and the PEG-IFN+Ribavirin programs), each patient followed for 1.5 years, or an event rate of approximately 1.5 deaths per 1000 patient years.

Reviewer Comment:

As mentioned above, given the new information provided by the sponsor in question 53 and the lack of any firm relationship (other than temporal) between receipt of Pegasys and onset of events leading to overdose, the overdose deaths cannot be generically attributed to receipt of Pegasys.

54. We are concerned about what appear to be high rates of serious infections in patients who received peginterferon alfa-2a. For example, in trial NV15496 there were 2 serious adverse events due to infections in the standard interferon group and a total of 12 serious adverse events due to infections in the patients who received pegylated interferon-alfa 2a. Also, in trial NV15497, there were three serious infections and one non-serious infection associated with Grade 4 neutropenia in patients who

received peginterferon alfa-2a. This trend has continued with the ongoing NV15942 study, wherein there has been one death due to sepsis, and three serious adverse events due to infection (*S. aureus* sepsis, sarcoidosis and *S. aureus* osteomyelitis). Please comment on these observations, and the apparent association between the use of peginterferon alfa-2a and serious infections. In addition, please provide further analyses of these data, including assessments of the relationship between infectious disease related adverse events and duration or degree of neutropenia, length of interferon therapy, or other risk factors, covariates, etc. that may help to better characterize this risk to patients receiving peginterferon alfa-2a.

The sponsor complied and performed an assessment of possible relationships between infectious disease related adverse events and (1) the duration or degree of neutropenia, (2) the length of interferon therapy and (3) any other risk factors in patients who developed serious infections during the monitoring period (treatment x 48 weeks and follow-up x 24 weeks) of the PEG-IFN vs. standard IFN clinical trials.

Results showed no predominance of types of infections or body system affected in the course of the infections, and responses to antimicrobial therapy appear to remain intact (i.e., patients generally responded to treatment of the event). Therefore, it was not obvious that the body's inherent ability to ward off infection appeared to be compromised.

Results also showed no correlation between onset of serious infection and degree or timing of neutropenia. There also did not appear to be a clustering of serious infections from a temporal standpoint.

Other risk factors explored included the existence of predisposing diseases and the virological response status. Approximately half of the patients who acquired a serious infection had a significant predisposing disease, but there was not a predominance for these diseases to point towards a risk factor from receipt of PEG-IFN. Regarding virologic response status, patients who developed a serious infection had the same general proportional response to either standard or PEG-IFN than the general HCV population in the clinical trials.

<u>Reviewer Comment</u>: The sponsor appears to have made a diligent attempt to ascertain whether any of relationship between infectious disease-related adverse events and duration or degree of neutropenia, length of interferon therapy or other risk factors existed for the serious infections that occur to a slightly higher frequency following treatment with PEG-IFN than following treatment with standard IFN. Perhaps the number of events and the post-hoc nature of such assessments prevented any risk factors from emerging from the analysis. Another possibility is that standard IFN itself induces a remarkable but less frequent incidence of serious infections. If this is the case, then perhaps a non-treatment control group would be necessary to maximize the signal from this event.

Although based on the negative findings, ----------, the fact of the higher incidence, even without a clear mechanism of toxicity, requires that labeling reflect the risk of serious infections as a result of PEG-IFN therapy.

55. Please provide additional clinical data (physician hospital summaries, autopsy findings [where appropriate], hematologic tests [where appropriate], and other physician generated summary documents) characterizing the clinical findings and course of the following patients:

a. 19153/0262
b. 20561/0369
c. 21713/0642
d. 19155/0321
e. 20862/0904
f. 20860/0075
g. 20993/1753
h. 20986/2431
i. 20983/2689
j. 20979/2649
k. 21208/2934
l. ---641
m. ----2335

55a. Death due to hepatic failure - This patient with ESLD received varying doses of PEG-IFN up to day 218 of the study. Doses were altered due to a number of complications of his ESLD as well as secondary to known adverse events associated with IFN products. Beginning on day 333, the patient began a downward spiral of events associated with ESLD that resulted in his death on day 397 of the study. His final demise began with a GI bleed secondary to chronic ITP (present at the time of admission to the study).

<u>Reviewer Comment</u>: The death does not appear to have been associated with use of PEG-IFN product, but rather the natural history of his ESLD.

55b. Overdose case, discussed in Question 52.

55c. Pneumonia case – This patient developed pneumonia while receiving Pegasys. The investigator assessed the pneumonia as being unrelated to the product. In response to the CR item, the sponsor submitted the hospital discharge summary for the patient.

<u>Reviewer Comment</u>: There was a temporal association between the use of Pegasys and the development of pneumonia. The patient was never neutropenic and had no other

evidence of an immune deficit that might have been induced by IFN. The patient was not re-challenged with IFN, so this potential evidence to indicate a causal association is also missing. Nevertheless, until more is known about potentially subtle but relevant mechanisms of IFN effect on immune functioning, a causal relationship of IFN to this event cannot be ruled out.

55d. Case of Idiopathic Thrombocytopenic Purpura – This patient developed ITP during the course of Pegasys treatment. The investigator assessed the reaction as possibly being related to study product. In response to the CR item, the sponsor submitted the hospital discharge summary for the patient, as well as lab and biopsy reports following the work-up for ITP.

Reviewer Comment: The temporal relationship of receipt of the pegylated interferon product with the onset of ITP is partial evidence of a causal relationship. There was no opportunity for re-challenge, however. Confounding factors include the occasional finding of ITP in patients with hepatitis C.

55e. Case of abdominal pain, rigors and pyrexia – This patient developed abdominal pain during the course of receiving IFN therapy that was serious enough for hospital admission. Coincidental thrombocytopenia was discovered and the patient received platelet transfusions. The source of the pain was never discovered. The patient received an empiric course of antibiotics to cover potential abdominal sources of bacteria. He responded well and was discharged from the hospital. The investigator judged this event as not related to IFN therapy. The sponsor provided an admission summary, a discharge summary and a narrative summary for review.

Reviewer Comment: Besides the temporal association of receipt of IFN, there is no other evidence to indicate IFN as a causal factor in this adverse event. The patient was never neutropenic and had no other evidence of an immune deficit that might have been induced by IFN. The patient was not re-challenged with IFN, so this potential evidence to indicate a causal association is also missing. Nevertheless, until more is known about potentially subtle but relevant mechanisms of IFN effect on immune functioning, a causal relationship of IFN to this event cannot be ruled out.

55.f Case of toxic shock syndrome - This patient developed a sepsis-like picture during the course of PEG-IFN treatment. The source may have been from skin abrasions. The patient responded to antibiotic therapy and was discharged from the hospital. PEG-IFN had been discontinued shortly after hospital admission and was not re-instituted. The investigator judged this event as not related to PEG-IFN therapy. The sponsor provided a discharge summary, laboratory results and a narrative summary for review.

Reviewer Comment: Besides the temporal association of receipt of PEG-IFN, there is no other evidence to indicate PEG-IFN as a causal factor in this adverse event. The

patient was never neutropenic and had no other evidence of an immune deficit that might have been induced by PEG-IFN. The patient was not re-challenged with PEG-IFN, so this potential evidence to indicate a causal association is also missing. Nevertheless, until more is known about potentially subtle but relevant mechanisms of PEG-IFN effect on immune functioning, a causal relationship of PEG-IFN to this event cannot be ruled out.

55g. Case of overdose: This patient had an intentional overdose of antidepressants while receiving IFN. She responded well to institution of different antidepressive medications. The investigator judged this event as probably related to IFN therapy. The sponsor provided a psychiatrist letter and a narrative summary for review.

Reviewer Comment: This adverse event is known to be associated with the use of all interferon products.

55h. Case of aortic aneurysm and post-operative wound infection – This patient had discontinued IFN (reason not given) 12 days before being hospitalized for a dissecting aortic aneurysm. Following surgery, the patient developed a post-operative infection. The investigator judged this event as not related to IFN therapy. The sponsor provided a discharge summary and a narrative summary for review.

Reviewer Comment: Besides the temporal association of receipt of IFN, there is no other evidence to indicate IFN as a causal factor in this adverse event. The patient was never neutropenic and had no other evidence of an immune deficit that might have been induced by IFN. The patient was not re-challenged with IFN, so this potential evidence to indicate a causal association is also missing. Nevertheless, until more is known about potentially subtle but relevant mechanisms of IFN effect on immune functioning, a causal relationship of IFN to this event cannot be ruled out.

55i. Case of heroin overdose – discussed by the sponsor as a part of response to question 52.

55j. Case of encephalitis – This patient developed a case of focal encephalitis while receiving PEG-IFN. No cause could be determined for the event; the investigator judged that the event was not related to receipt of the PEG-IFN. The sponsor provided a discharge summary and a narrative summary for review.

Reviewer Comment: The temporal relationship of receipt of the pegylated interferon product with the onset of encephalitis is partial evidence of a causal relationship. There was no opportunity for re-challenge, however, to help confirm this. Based on findings that IFN is capable of shifting T helper cell function towards development of TH1 subsets, it is biologically plausible that this autoimmune event is related to PEG-IFN.

55k. Case of autoimmune hepatitis – This patient developed a case of autoimmune hepatitis while receiving PEG-IFN. No cause could be determined for the event; the

investigator judged that the event may have possibly been associated with receipt of the PEG-IFN. The sponsor provided a discharge summary, laboratory results and a narrative summary for review.

Reviewer Comment: The temporal relationship of receipt of the pegylated interferon product with the onset of autoimmune hepatitis is partial evidence of a causal relationship. There was no opportunity for re-challenge, however. Based on findings that IFN is capable of shifting T helper cell function towards development of TH1 subsets, it is biologically plausible that this autoimmune event is related to PEG-IFN.

55 l. Case of septic shock – This unfortunate patient developed sepsis subsequent to infection of a splinter. The patient was receiving PEG-IFN at the time of infection and had developed neutropenia. The investigator judged that the event was possibly related to receipt of PEG-IFN. The sponsor provided an autopsy report and a narrative summary for review.

Reviewer Comment: The temporal relationship of receipt of the pegylated interferon product with the onset of sepsis is partial evidence of a causal relationship. The development of neutropenia that was apparently induced by PEG-IFN would appear to have been a contributing factor to this event.

55m. Overdose case, discussed in Question 52.

56. Several issues pertinent to clarifying the safety and effectiveness of peginterferon alfa-2a require additional information that may be obtained from postmarketing studies. We request that you propose additional clinical studies to address the following issues:

    a. Please provide a plan to evaluate the pharmacokinetics and pharmacodynamics of methadone in patients who received peginterferon alfa-2a.
    b. The data submitted in your license application do not adequately address the safety and efficacy of peginterferon alfa-2a in various ethnic groups, as over 90 percent of study participants were Caucasians. Please provide a plan to more extensively evaluate the safety and efficacy of peginterferon alfa-2a in various ethnic subgroups.

    For each of the above studies, please submit:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed

- A proposed timeline for conducting the study, including all major milestones for the study, e.g., submission of finalized protocol to the FDA, completion of patient accrual, completion of the study, and submission of the final report, ---- datasets and applicable revised labeling to the FDA.

a. Methadone Drug Interaction Study

To comply with this item, the sponsor submitted study protocol NP16048 entitled "The pharmacokinetic and pharmacodynamic effects of the concomitant administration of methadone and peginterferon alfa-2a in chronic hepatitis C patients receiving methadone maintenance therapy."

The study will enroll 24 patients who have CHC and are IVDU who are on a methadone maintenance program. The patients will be assessed for methadone PK parameters before and after single and multiple (four) doses of Pegasys + Ribavirin (the study will take place in the context of the preliminary results of a superior efficacy of PEG-IFN + Ribavirin, therefore for ethical reasons, the Pegasys product will not be given alone). Besides PK of methadone, Pegasys and ribavirin, possible pharmacodynamic interactions will be assessed by comparing the ability of the regimens (vs. historical data in CHC patients and healthy controls) to induce the biomarker 2',5'-oligoadenylate synthetase.

Reviewer Comment: The design of the proposed study is adequate to address the issue in this item.

b. Ethnic Group Studies

To comply with this item, the sponsor submitted study protocol NR16172 entitled "A multicenter, open-label study investigating the efficacy of Pegasys in combination with ribavirin as initial treatment of CHC in non-Hispanic African-American HCV genotype 1 patients as compared to non-Hispanic Caucasian HCV genotype 1 patients."

The study will enroll 108 African-Americans and 28 Caucasian-Americans who have infection with HCV genotype 1. Patients will be treated with Pegasys + Ribavirin (the study will take place in the context of the preliminary results of a superior efficacy of PEG-IFN + Ribavirin, therefore for ethical reasons, the Pegasys product will not be given alone) for 48 weeks. Sustained viral response will be the primary outcome measure. Liver biopsy before and after therapy will also be assessed.

Reviewer Comment: The design of the proposed study is adequate to address the issue in this item. The design is especially valuable since genotype 1 is not only the most recalcitrant to anti-viral therapy, but this genotype is the most prevalent in the African-American population.

To additionally comply with this item, the sponsor compiled the global database of the product's use (in the Phase 3 studies) in Oriental-Americans and compared sustained viral response rates in this group versus Caucasian-Americans and African-Americans.

Reviewer Comment: Upon review of these data, of note is the finding that Oriental-Americans tended to have a higher SVR (47%) than Caucasian-Americans (34%) and African-Americans (15%). The lower virological response in African-Americans compared with the other groups was not a result of a higher frequency of dose modification or discontinuation for adverse events.

3.0 REVIEWER CONCLUSIONS

The sponsor has adequately responded to all of the items in the Complete Response Letter. The information provided, as well as data from the original BLA, will be consolidated for entry into the product label.

4.0 REVIEWER RECOMMENDATIONS

Pegylated Interferon alfa-2a is recommended to be approved for licensure in the United States.

Submitted by:

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Mark O. Thornton, M.D., M.P.H., Ph.D. Date
Medical Officer
Food and Drug Administration,
Center for Biologics Evaluation and Research